REMARKS

This Amendment is filed in response to the Advisory Action dated June 30, 2006 and the Final Office Action dated January 12, 2006. Entry of this amendment is requested, with a request for continued examination accompanying this amendment.

Claims 1-13 are pending, with claims 14-94 being cancelled. Claim 1 is amended herein to recite a PHA yield as indicated, with support being found in the specification at, e.g., page 92, line 6.

Claims 1-13 stand rejected for obviousness in light of Madison et al., Johnston et al., Clemente et al., and Linde et al. The Advisory Action explained that yeast are known to grow anaerobically and that Linde et al. teaches that the transcript profiles of yeast have little difference in anaerobic versus aerobic conditions. Thus, if PHA production is known under aerobic conditions, then PHA production would be expected under anaerobic conditions. This argument assumes, among other things, that equivalent transcript profiles in aerobic and anaerobic conditions would be predictive of success.

Respectfully, however, the teachings of Linde et al. are largely irrelevant to the production of PHA, as explained below. Further, as explained below, artisans in this field have clearly stated that metabolic engineering is an unpredictable art such that there could not be any reasonable expectation of success with the claimed anaerobic production of PHA. Moreover, the motivation provided for combining the prior art is believed to be fatally defective, as explained below. Therefore it is respectfully submitted that no prima facie case of obviousness has been made, so that withdrawal of these rejections is requested.

Moreover, as explained in detail below, an artisan familiar with what is taught in this field would expect that anaerobic production of PHA as claimed would probably *not* be successful since such an artisan would expect that the NADPH/NADP cycle that is crucial to PHA production would likely *not* be available during anaerobic fermentation so

that PHAs would not be produced. And such an artisan would *not* accept the premise that aerobic production of PHA was a predictor of anaerobic PHA production because the cells' metabolic pathways are quite different in aerobic versus anaerobic processes.

An invention is not obvious when the relevant literature states that the achieving the invention is unpredictable.

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. MPEP 2143.02. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. MPEP 2143.02. In the case *Amgen v. Chugai*, 927 F.2d 1200,(C.A.F.C. 1991) the court upheld a finding of nonobviousness since there would have been "**no more than a fifty percent chance of success**" in cloning the disputed EPO gene using prior art methods. 927 F.2d 1200, 1208. The court further pointed to the well established principle that "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." 927 F.2d 1200, 1208. Even though it found that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success. 927 F.2d 1200, 1208, 1209, which also cited *In re O'Farrell*, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (C.A.F.C. 1988).

In the present case, as discussed below, the literature states that these are unpredictable arts such that there would be no reasonable expectation of success. Therefore the rejection of the claims can not stand.

An invention is not obvious when the cited references do no more than suggest it would be obvious to try to make the invention.

"The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to

try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. [citations omitted]. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. [citations omitted]" *In Re O'Farell*, 853 F.2d 894, 903 (C.A.F.C. 1988). As cited above, both the motivation to combine prior references and the expectation of success must be founded in the prior art.

In this case, the Patent Office provides motivation to combine the references as a desire to: (a) increase the efficiency of PHA production from yeast or (b) to determine if genes involved in PHA synthesis have different transcript profiles under aerobic or anaerobic conditions (as stated at pages 5-6 of the January 2006 Office Action). With respect to argument (a): The record does not show any prior art suggestion that anaerobic conditions would increase efficiencies: withdrawal of this argument or clarification of this point is requested. Argument (b) is merely a suggestion that anaerobic fermentations should be tried to see what would happen: this is mere speculation about what scientists might like to try out and is not based on the prior art; indeed, one could make the assumption that scientists are curious about everything and that anything would be an interesting experiment: such reasoning would, respectfully, be absurd. Arguments that are not based on the prior art are mere hindsight and can not stand; therefore this argument (b) should be withdrawn.

Further, the Patent Office explains that argument (b) rests on the proposition that "Linde et al. teaches little difference of aerobic and anaerobic transcript profiles of S. cervesiae" (see sentence bridging page 5-6 of January 2006 Office Action) and that an artisan would therefore be motivated to determine if genes involved in PHA synthesis have different transcript profiles under aerobic or anaerobic conditions". This statement

by the Patent Office is **an admission that the cited references do not predict success for the claimed invention.** If Linde et al. stands for the proposition that the gene profiles are expected to be the same under both conditions, then the very same reference would not motivate testing the profiles to see if they might turn out to be the same.

The suggested motivations to combine the references are only, at best, assertions that it would have been obvious to try to make the claimed invention. The rejections fall short of pointing to a reason for actually doing the experiments that the Applicants had to do to discover the claimed invention.

Production of PHA by engineering of metabolic pathways is an unpredictable art

The literature explicitly states that these are unpredictable arts such that there would be no reasonable expectation of success for making the claimed invention. Madison et al. state that "Taken together, these molecular genetic data provide a glimpse of the complexity of PHA metabolism. Since PHA formation **is dependent on the fluxes in central metabolic pathways and the levels of precursors,** a detailed knowledge of the molecular physiology of PHA metabolism is ***critical*** for successful implementation of transgenic PHA producers. ***Unlike the production of heterologous proteins, which relies mostly on sufficient gene expression***, recombinant PHA production involves coordinated expression of heterologous enzymes over a prolonged period and with a concomitant redirection of the metabolism of the host. As a consequence of the metabolic changes introduced by expressing the *pha* and *phb* genes, the cell will induce its own responses, *which are not necessarily favorable for PHA production.* It is therefore ***critical*** to understand how bacteria normally **regulate PHA formation** and how undesired responses from a recombinant host can be prevented. ***Only then*** can recombinant processes be successfully developed and lead to what are expected to be the most efficient PHA production processes." Madison et al, at page 35 under "Conclusions", emphases added.

These arts are related to metabolic pathway engineering and not to merely getting an organism to express some number of heterologous proteins. It is one thing to have a few heterologous proteins expressed but quite another to have any meaningful amount of PHA produced, e.g., the claimed at 1.5% of dry cell weight. The metabolic changes introduced by expressing the appropriate genes, the cell will induce its own responses, which are not necessarily favorable for PHA production. **Madison et al. explains that merely expressing certain genes does not provide even a *punctilio* of predictability for PHA production.**

For these reasons, the literature states that these are unpredictable arts such that there would be no reasonable expectation of success. Therefore the rejection of the claims can not stand.

The teachings of Linde et al are irrelevant to predicting success of production of PHA in anaerobic cultures

The teachings of Linde et al are irrelevant to predicting success of production of PHA in anaerobic cultures because Linde et al. is directed to the production of heterologous proteins, but what is claimed involves redirection of the metabolism of the host - not merely the expression of particular genes. PHA is an intermediate metabolite. Production of PHA depends on the presence of certain enzymes and also, among other things, a high ratio of NADPH to NADP (see discussion, below). Therefore the presence of certain enzymes is not an adequate basis to predict PHA production. The Patent Office has argued that Linde predicts the presence of certain enzymes. The Examiner's argument is not therefore not an adequate basis to predict PHA production: merely having certain enzymes present is not enough. As explained in the passage of Madison et al. quoted above, even if Linde et al. were assumed to predict the success of expression of certain proteins, **this would not be enough to predict success** because it does not speak to the critical aspects of the cell's metabolic pathways. Thus Linde et al. is largely

irrelevant because it does not address factors that the literature states are critical to success. Accordingly, withdrawal of the obviousness rejection is requested on the grounds that no prima facie case of obviousness has been made.

An artisan would not have reasonably expected anaerobic fermentation to be a successful process for PHA production. Further, the Applicant's claimed method is surprising and contrary to conventional wisdom.

It is respectfully submitted that the arguments, above, provide multiple reasons for withdrawal of the rejection. Moreover, the Applicant is entitled to a patent unless there is evidence logically developed from the prior art for not granting the patent. Nonetheless, there are further aspects to the claimed invention that provide additional evidence of its patentability. One aspect is that an artisan, before reading the Application, would not have reasonably expected anaerobic fermentation to successfully produce any appreciable amount of PHA, i.e., the claimed at least 1.5% PHA per dry cell weight.

Among other factors, the ratio of NADPH to NADP is key for PHA production, with a high ratio favoring PHA production.[1] NADPH is formed primarily through operation of the pentose phosphate cycle and the prior art does not indicate how much of the metabolism is directed into this cycle, or how to reliably predict how this metabolism will be directed.

Moreover, as explained in the section of the Application entitled "Transhydrogenase Systems" on page 21, cellular metabolism must maintain the redox balance of the cell if the cell is to survive. In aerobic fermentation processes, oxygen is

[1] "The availability of reducing equivalents in the form of NADPH is therefore considered to be the driving force for P(3HB) formation." Linde et al., page 27, last sentence of first paragraph.

available to serve as an electron sink to carry away excess H ions in the form of water. This prevents electrons from building up in the electron transport system. In anaerobic processes, however, the elimination of the H ion is much more problematic. The production of ethanol in yeast is driven by the need to "find" an electron sink that is an alternative to oxygen. The cell's change from aerobic to anaerobic culture is a dramatic change that affects its metabolic pathways in many aspects. While many proteins essential to cell survival might be expressed at the same levels, the metabolism of the cell has to be significantly re-oriented to cope with a lack of oxygen. PHA and ethanol are both metabolites and not heterologous proteins expressible by the familiar mechanisms of genetic engineering. When culture conditions are dramatically changed, predicting which metabolites will be favored is quite problematic, as explained in Madison et al., quoted above.

In the case of PHA production, it was quite problematic to contemplate successfully producing a metabolite that depends on NADPH/NADP ratios under conditions that are known to re-orient the cells to offload excess H ions as ethanol, i.e., in anaerobic culture. As already stated, it was quite unpredictable. In this case, when the cell's metabolic machinery is dedicated to making ethanol for survival, trying to intervene in that path to divert resources to making PHA seemed counterintuitive. And, crucially, yeast cells must maintain a delicate balance between NADPH and NADH production and consumption to maintain their redox balance. While many cells have a transhydrogenase system that permits interconversion between NADPH and NADH, it is conventionally believed that yeast do not have this capability. See Application, "Transhydrogenase Systems" on page 21.

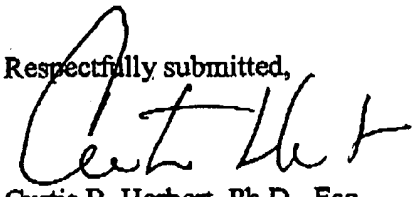
Surprisingly, however, the results in the Application suggest that PHA can serve as a sink for electrons (NADH) during anaerobic metabolism. This is in contrast to a normal fermentation product that is excreted from the cell. Conventional wisdom provides no prediction of this capability and has no ready explanation. Evidently,

however, PHA can substitute for a normal fermentation product and accumulate as a fermentation product substitute within the cell. This result implies at the same time that there is a mechanism to convert the excess NADH into NADPH to enable PHA synthesis, despite the fact that there is no conventionally known transhydrogenase system for their interconversion. Alternately this could indicate that perhaps NADH can be directly used for intracellular PHA formation. In hindsight, using PHA as an electron sink seems like a "smart" move for the yeast cells, but of course the question was never how "smart" the cells were, but if their metabolic machinery could possibly tolerate PHA production. For all of these reasons, an artisan would not have reasonably expected anaerobic fermentation to be a successful process for PHA production.

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,



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